Home versus in-hospital treatment of outpatients with acute deep venous thrombosis of the lower limbs

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Background: **Some physicians are still concerned about the safety of treatment at home of patients with acute deep venous thrombosis (DVT).**
Methods: **We used data from the RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry to compare the outcomes in consecutive outpatients with acute lower limb DVT according to initial treatment at home or in the hospital. A propensity score-matching analysis was carried out with a logistic regression model.**
Results: **As of December 2012, 13,493 patients had been enrolled. Of these, 4456 (31%) were treated at home. Patients treated at home were more likely to be male and younger and to weigh more; they were less likely than those treated in the hospital to have chronic heart failure, lung disease, renal insufficiency, anemia, recent bleeding, immobilization, or cancer. During the first week of anticoagulation, 27 patients (0.20%) suffered pulmonary embolism (PE), 12 (0.09%) recurrent DVT, and 51 (0.38%) major bleeding; 80 (0.59%) died. When only patients treated at home were considered, 12 (0.27%) had PE, 4 (0.09%) had recurrent DVT, 6 (0.13%) bled, and 4 (0.09%) died (no fatal PE, 3 fatal bleeds). After propensity analysis, patients treated at home had a similar rate of venous thromboembolism recurrences and a lower rate of major bleeding (odds ratio, 0.4; 95% confidence interval, 0.1-1.0) or death (odds ratio, 0.2; 95% confidence interval, 0.1-0.7) within the first week compared with those treated in the hospital.**
Conclusions: **In outpatients with DVT, home treatment was associated with a better outcome than treatment in the hospital. These data may help safely treat more DVT patients at home. (J Vasc Surg 2014;59:1362-7.)**

Current guidelines of antithrombotic therapy recommend initial treatment of patients with acute deep venous thrombosis (DVT) with low-molecular-weight heparin (LMWH), fondaparinux, or unfractionated heparin (UFH) over no such initial therapy.[1] A number of studies comparing LMWH administered at home (without hospital admission or after early discharge) with UFH in the hospital suggested that home therapy may be associated with improved outcome and better quality of life.[2-12] Hence, in DVT patients with adequate home circumstances, current guidelines recommend that most patients with DVT be initially treated at home rather than in the hospital.[1] However, many physicians are still concerned about the safety of home therapy because even with adequate anticoagulation, some patients may present with symptomatic pulmonary embolism (PE), recurrent DVT, major bleeding complications, or even death.

The RIETE (Registro Informatizado de la Enfermedad TromboEmbólica) registry is an ongoing, international (Spain, France, Italy, Israel, Germany, Switzerland, Republic of Macedonia, and Brazil), multicenter, prospective registry of consecutive patients presenting with symptomatic acute venous thromboembolism (VTE). It started in Spain in 2001, and some years later, the database was translated into English to expand the Registry to other countries, with the aim to help physicians worldwide select the most appropriate therapy for their patients. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, major bleeding, and mortality, and risk factors for these outcomes.[13-16] The current analysis compared the outcome of outpatients with acute DVT of the lower limbs within the first week of anticoagulation according to initial therapy at home or in the hospital.

METHODS

Consecutive patients presenting with symptomatic acute DVT confirmed by objective tests (compression ultrasonography or contrast venography) were enrolled in

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RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

In the RIETE registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded onto a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigned patients a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared the submitted data with medical records.

Study design. For this study, all outpatients with acute DVT in the lower limbs, with no respiratory symptoms suggesting PE, and initially treated with LMWH or fondaparinux were considered. Those initially treated with UFH, thrombolytics, rivaroxaban, or dabigatran were excluded; also excluded were those undergoing an inferior vena cava filter and those not receiving anticoagulation. Home therapy was considered when patients spent less than 24 hours in the hospital from their arrival to the emergency department. The major outcome for this study was the development of symptomatic and objectively confirmed PE, recurrent DVT, major bleeding, or death within the first 7 days of treatment. Secondary outcomes were fatal PE or fatal bleeding appearing within the first 7 days. Recurrent DVT was defined as either the extension of the index DVT (in the ipsilateral leg) or a new DVT appearing in the contralateral leg. In the absence of autopsy, fatal PE was defined as any death within 10 days of a confirmed PE diagnosis, in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. Major bleeding was defined as an overt bleed that required a transfusion of 2 units or more of blood; was retroperitoneal, spinal, or intracranial; or was fatal.

Baseline variables. The following clinical variables were recorded when the qualifying episode of DVT was diagnosed: patient's sex, age, and body weight; presence of coexisting conditions, such as chronic heart or lung disease; recent (<30 days before DVT) major bleeding; presence of risk factors for DVT, including active cancer (defined as newly diagnosed cancer or cancer that is being treated [ie, surgery, chemotherapy, radiotherapy, hormonal or support therapy]), recent immobilization (defined as nonsurgical patients who were confined to bed with bathroom privileges for ≥4 days in the 2 months before DVT diagnosis), and surgery (defined as those who had undergone surgery in the 2 months before DVT); extent of the DVT (distal DVT was DVT confined to the infrapopliteal veins); and laboratory data, including whole blood cell counts and serum creatinine clearance levels. Creatinine clearance levels at baseline were measured according to the Cockcroft and Gault formula.[17]

Treatment and follow-up. In RIETE, there was no standardization of treatment, and patients were managed according to the clinical practice of each participating hospital. The type, dose, and duration of anticoagulant therapy were recorded. Patients were followed up for at least 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting DVT or PE recurrences or bleeding complications were recorded. Each episode of clinically suspected PE or recurrent DVT was investigated by repeated ultrasonography, contrast venography, lung scanning, helical computed tomography, or pulmonary angiography as appropriate. Most outcomes were classified as reported by the clinical centers, but if staff at the coordinating center were uncertain how to classify a reported outcome, that event was reviewed by a central adjudicating committee (<10% of events).

Statistical analysis. We used Student *t*-test and χ^2 test (or Fisher exact test where appropriate) to compare continuous and categorical variables, respectively, between patients treated at home and those treated in the hospital. We then carried out a propensity score-matching analysis by a logistic regression model including the clinical characteristics of the patients, risk factors for VTE, and underlying diseases to get the propensity score to be treated at home vs in the hospital.[18-20] With use of the psmatch2 for Stata program, 4455 patients treated at home (of 4456) were matched with those treated in the hospital. We carried out a greedy method (nearest neighbor method) to get the unbiased matched pairs of patients with a ratio of 1:1 (1 case [home therapy] and 1 control [in hospital] were matched) without replacement, using a caliper of 0.2 times the standard deviation of propensity score. Propensity score matching is optimal to produce the largest similarity within matched groups, but because matching on the propensity score may not balance for unobserved confounders, a sensitivity analysis was performed evaluating several caliper widths iteratively until between-group standardized differences were minimized. To validate the success of the matching procedure, standardized differences were measured (in percentage points) in observed confounders between matched groups.

Finally, we carried out a multivariable analysis through a conditional logistic regression model with all matched pairs to determine whether home therapy (vs in hospital) was independently associated with a worse outcome at 7 and 90 days. We calculated adjusted odds ratios (ORs) (and 95% confidence intervals [CIs]) by controlling for relevant covariates by means of multiple logistic regression analysis. Covariates entering in the model were selected by a significance level of $P < .20$ on univariable analysis or by a well-known association reported in the literature. We did not include the dose of LMWH received because its choice was expected to have been influenced by the physician's assessment of a patient's risk of bleeding or recurrent

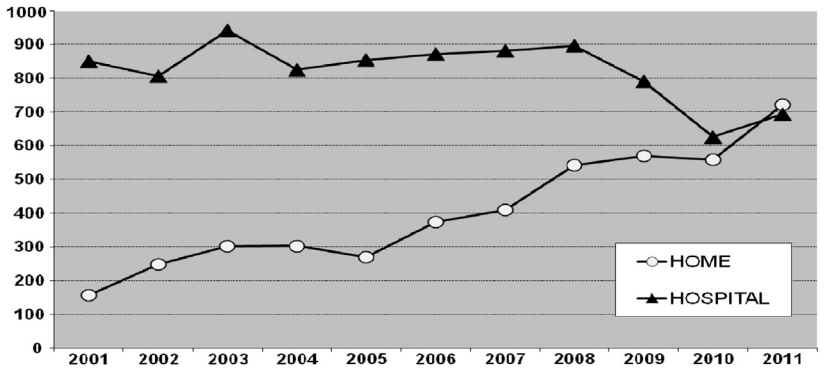

Fig. Annual rates of patients treated at home or in the hospital over time.

VTE. We did not include any variables obtained during follow-up that were not available at baseline. We used SPSS software (version 20; SPSS Inc, Chicago, Ill) and Stata program (with the psmatch2 package; Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. 2003) for the statistical management of the data, and considered a two-sided $P < .05$ to be statistically significant.

RESULTS

As of December 2012, 44,085 VTE patients were enrolled in RIETE. Of these, 13,742 were outpatients presenting with acute DVT in the lower limbs and no respiratory symptoms suggesting PE. As initial therapy, 13,271 (97%) patients received LMWH, 222 (1.6%) fondaparinux, 218 (1.6%) UFH, 19 rivaroxaban, and 12 thrombolytics. In all, 13,493 (31%) patients received initial therapy with LMWH or fondaparinux and did not undergo a vena cava filter. They were the subject for the current analysis.

Overall, 4456 patients (33%) were treated at home with no hospital admission. For patients admitted to the hospital, mean duration of hospital stay was 10.5 days (95% CI, 8.5-12.5). Median duration was 6 days (interquartile range, 0-12 days).The proportion of patients treated at home progressively increased over time, but one in every two patients was still initially treated in the hospital in 2012 (Fig). Patients treated at home were more likely to be male and significantly younger and to weigh more; they were less likely to have chronic heart failure, chronic lung disease, renal insufficiency, anemia, recent major bleeding, recent immobilization, or cancer (Table I). The majority of patients in both groups (97% vs 99%) received initial therapy with LMWH; then, most (71% vs 74%) switched to vitamin K antagonists. Interestingly, patients treated at home were treated with lower daily doses of LMWH than were those treated in the hospital. The duration of LMWH use was longer in patients initially treated at home than in those admitted to the hospital; mean values were 14 ± 26 days vs 11 ± 36 days ($P < .001$). Median values were 8 vs 7 days ($P < .001$).

On logistic regression analysis, the following variables were found to influence the decision to treat patients at home vs in the hospital (C-statistic value, 0.68; 95% CI, 0.67-0.69): age, chronic lung disease, renal insufficiency, anemia, leukocytosis, recent major bleeding, recent immobilization ≥4 days, prior VTE, proximal DVT, and year of diagnosis. After propensity score matching, all these variables became similar in both groups.

Overall, 27 patients (0.20%) experienced symptomatic PE (7 were fatal), 12 (0.09%) had recurrent DVT, 51 (0.38%) bled (13 were fatal), and 80 (0.59%) died within the first week of therapy (Table II). Patients treated at home had a significantly lower rate of major bleeding events (OR, 0.3; 95% CI, 0.1-0.6) and a lower mortality (OR, 0.1; 95% CI, 0.04-0.3) than those treated in the hospital had, with a similar rate of VTE recurrences. Among 4456 DVT patients treated at home, 4 (0.09%) died within the first 7 days; 3 died of bleeding, 1 of disseminated malignant disease. Among 9037 patients initially treated in the hospital, 76 (0.84%) died within the first week. The causes of death were as follows: disseminated cancer, 23; respiratory insufficiency, 13; infection, 9; bleeding, 7; PE, 6; bronchoaspiration, 4; renal insufficiency, 2; heart failure, 2; sudden unexpected death, 2; multiorgan failure, 2; myocardial infarction, 1; bowel occlusion, 1; unknown, 4. During the first 3 months, 95 patients (0.70%) had developed PE (21 were fatal), 139 (1.03%) had recurrent DVT, 188 (1.39%) bled (43 were fatal), and 672 (4.98%) died. Patients treated at home still had a significantly lower rate of major bleeding and a lower mortality than those treated in the hospital had. In addition, the rate of fatal PE was also significantly lower at 90 days in patients treated at home (OR, 0.1; 95% CI, 0.01-0.8).

After propensity analysis, patients receiving treatment at home had a significantly lower rate of major bleeding complications (OR, 0.4; 95% CI, 0.1-1.0) and a lower mortality (OR, 0.2; 95% CI, 0.1-0.7) during the first week compared with those treated in the hospital (Table III). At the end of the third month, patients treated at home had a significantly lower rate of fatal PE (OR, 0.1; 95% CI, 0.01-0.9) and a lower mortality (OR, 0.4; 95% CI, 0.3-0.5).

Table I. Clinical characteristics and treatment, according to therapy in the hospital or at home

	Home therapy (n = 4456)	*In-hospital therapy (n = 9037)*	*OR (95% CI)*	P *value*
Clinical characteristics				
Gender, male	2412 (54)	4611 (51)	1.1 (1.1-1.2)	.001
Age, years	62 ± 17	66 ± 18	—	<.001
Body weight, kg	77 ± 15	74 ± 15	—	<.001
Underlying conditions				
Chronic heart failure	151 (3.4)	388 (4.3)	0.8 (0.6-0.9)	.01
Chronic lung disease	303 (6.8)	846 (9.4)	0.7 (0.6-0.8)	<.001
Creatinine clearance levels, mL/min	82 ± 35	71 ± 33	—	<.001
Anemia	1084 (24)	3047 (34)	0.6 (0.6-0.7)	<.001
Recent major bleeding	24 (0.5)	103 (1.2)	0.5 (0.3-0.7)	.001
Risk factors for VTE				
Postoperative	378 (8.5)	806 (8.9)	0.9 (0.8-1.1)	.40
Immobility ≥4 days	894 (20)	2311 (26)	0.7 (0.7-0.8)	<.001
Cancer	769 (17)	1775 (20)	0.9 (0.8-0.9)	.001
None of the above	2643 (59)	4732 (52)	1.3 (1.2-1.4)	<.001
Prior VTE	729 (16)	1534 (17)	1.0 (0.9-1.1)	.37
Initial DVT presentation				
Proximal DVT	3371 (76)	7573 (84)	0.6 (0.6-0.7)	<.001
Bilateral lower limb DVT	93 (2.1)	246 (2.7)	0.8 (0.6-1.0)	.03
Initial therapy				
LMWH	4317 (97)	8954 (99)	0.3 (0.2-0.4)	<.001
LMWH dose, IU/kg/d	164 ± 42	180 ± 39	—	<.001
Fondaparinux	139 (3.1)	83 (0.9)	3.5 (2.6-4.6)	<.001
Long-term therapy				
Vitamin K antagonists	3139 (71)	6601 (74)	0.8 (0.8-0.9)	<.001
LMWH	1207 (27)	2233 (25)	1.1 (1.0-1.2)	.009
LMWH dose, IU/kg/d	138 ± 48	142 ± 51	—	.04

CI, Confidence interval; *DVT,* deep venous thrombosis; *IU,* international units; *LMWH,* low-molecular-weight heparin; *OR,* odds ratio; *SD,* standard deviation; *VTE,* venous thromboembolism.
Continuous data are presented as mean ± standard deviation and categoric data as number (%).

Table II. Clinical outcome, according to treatment in the hospital or at home

	Home therapy (n =4456), No. (%)	*In-hospital therapy (n = 9037), No. (%)*	*OR (95% CI)*	P *value*
7-day outcome				
Symptomatic PE	12 (0.27)	15 (0.17)	1.6 (0.8-3.5)	.21
Recurrent DVT	4 (0.09)	8 (0.09)	1.0 (0.3-3.4)	.98
Major bleeding	6 (0.13)	45 (0.50)	0.3 (0.1-0.6)	.001
Overall death	4 (0.09)	76 (0.84)	0.1 (0.04-0.3)	<.001
Fatal PE	0	7 (0.08)	—	.06
Fatal bleeding	3 (0.07)	10 (0.11)	0.6 (0.2-2.2)	.45
90-day outcome				
Symptomatic PE	37 (0.83)	58 (0.64)	1.3 (0.9-2.0)	.22
Recurrent DVT	39 (0.88)	100 (1.11)	0.8 (0.5-1.1)	.21
Major bleeding	39 (0.88)	149 (1.65)	0.5 (0.4-0.8)	<.001
Overall death	72 (1.62)	600 (6.64)	0.2 (0.2-0.3)	<.001
Fatal PE	1 (0.02)	20 (0.22)	0.1 (0.01-0.8)	.006
Fatal bleeding	7 (0.16)	36 (0.40)	0.4 (0.2-0.9)	.02

CI, Confidence interval; *DVT,* deep venous thrombosis; *OR,* odds ratio; *PE,* pulmonary embolism.

DISCUSSION

Current guidelines on antithrombotic therapy recommend initial treatment at home over treatment in the hospital for DVT patients with adequate home circumstances.[1] Our data revealed that in real life, only one in every three patients was treated at home, thus suggesting that many physicians are still concerned about the risks of home therapy. Certainly, the proportion of patients treated at home progressively increased during the 10-year period, but 1 in every 2 patients was still initially treated in the hospital in 2012, as also found in other recent studies.[21] Our data revealed that patients treated at home did not experience a worse outcome than those treated in the hospital did. In fact, they had fewer major bleeding events and a lower mortality. Because patients in both groups were mostly at home by 7 days, any difference in outcome between groups should be attributed to the fact that patients who were

Table III. Clinical outcome after propensity score matching

	Univariable		*Multivariable*	
	OR (95% CI)	P *value*	*OR (95% CI)*	P *value*
7-day outcome				
Symptomatic PE	2.4 (0.8-6.8)	.10	2.4 (0.8-6.8)	.10
Recurrent DVT	0.7 (0.2-2.4)	.53	0.7 (0.2-2.4)	.56
Major bleeding	0.4 (0.1-1.0)	.04	0.4 (0.1-1.0)	.04
Overall death	0.2 (0.1-0.7)	.009	0.2 (0.1-0.7)	.01
Fatal PE	—	—	—	—
Fatal bleeding	1.5 (0.3-9.0)	.66	1.6 (0.3-9.3)	.63
90-day outcome				
Symptomatic PE	1.3 (0.8-2.1)	.33	1.3 (0.8-2.1)	.34
Recurrent DVT	0.7 (0.5-1.1)	.12	0.7 (0.5-1.1)	.12
Major bleeding	0.8 (0.5-1.2)	.34	0.9 (0.6-1.4)	.56
Overall death	0.4 (0.3-0.5)	<.001	0.4 (0.3-0.5)	<.001
Fatal PE	0.1 (0.01-0.9)	.04	0.1 (0.01-0.9)	.04
Fatal bleeding	1.0 (0.4-2.9)	1.00	1.0 (0.4-2.9)	.99

CI, Confidence interval; *DVT,* deep venous thrombosis; *OR,* odds ratio; *PE,* pulmonary embolism.

initially treated in the hospital were medically sicker than those treated at home.

During the first 7 days of anticoagulation, patients receiving treatment at home had a similar rate of PE events (0.27% vs 0.17%), a significantly lower rate of major bleeding (0.13% vs 0.50%), and a lower mortality (0.09% vs 0.84%) compared with those treated in the hospital. The lower rate of major bleeding may have been due to an appropriate identification of patients perceived to be at high risk for bleeding and the lower LMWH doses administered to patients treated at home. The similar rate of PE events in patients in both groups reveals the difficulties in identifying at-risk patients. The lower mortality in patients treated at home may not be explained only because these patients were younger or had fewer comorbidities; any difference in baseline characteristics had likely disappeared after propensity score matching. Clinical experience of attending physicians may have been of help to identify low-risk patients to be treated at home. Interestingly, at the end of the third month, patients receiving treatment at home from the beginning still had a lower mortality and a lower rate of symptomatic PE, even after propensity score matching and multivariable analysis.

In the literature, six randomized clinical trials involving 1708 participants compared home with in-hospital therapy for patients with acute DVT. As in our study, patients treated at home with LMWH had fewer VTE recurrences (relative risk [RR], 0.61; 95% CI, 0.42-0.90) and major bleeding events (RR, 0.67; 95% CI, 0.33-1.36) and a lower mortality (RR, 0.72; 95% CI, 0.45-1.15) than those treated in the hospital with UFH or LMWH had.[6] In addition, treatment at home was cost-effective and preferred by most patients. However, all these studies had some methodological problems, such as high exclusion rates, partial hospital treatment of many patients receiving LMWH, and comparison of UFH in the hospital with LMWH at home. Our study compared consecutive patients (there were no exclusion criteria) receiving similar therapies and confirmed that home therapy was associated with a better outcome.

Our findings may have several limitations. First, for this study, home therapy was considered when patients spent less than 24 hours in the hospital from their arrival to the emergency department. Certainly, it would be interesting to compare different durations of hospital stay, but there is no way to do it with the RIETE database. We gather information on the date of arrival and the date of discharge, not the hours of admission and discharge. Second, in RIETE, we differentiate only between proximal (above the popliteal vein) and distal DVT. Therefore, there is no information on the more proximal thrombus extent (ie, femoral vs iliac vs caval). Third, in the RIETE registry, there is no information on the type of LMWH used, how it was dosed, and whether it was administered once a day or twice a day. We gathered only the daily dose. Fourth, selection bias could have skewed the study sample because RIETE is a registry and patients were not randomly allocated but received the prescription of their physician's choice.[14] Finally, every physician had different forms of approach to home vs in-hospital therapy, and some patients may not have been properly trained to follow the recommended guidelines for treatment of DVT. However, the broad range of patients with acute DVT from multiple centers, countries, and treatment settings enrolled in the RIETE registry decreased the likelihood of the inclusion of a skewed population in this study. Our population-based sample reflected the effects of home therapy in "real-world" clinical care and enhanced the generalizability of our findings. Moreover, we used propensity score matching to make the patient groups comparable according to the potential confounders, and we successfully balanced the observed differences. However, residual confounding may still have occurred. Finally, the similar findings obtained at 7 and 90 days provided evidence of the robustness of the study and further strengthened the soundness of our conclusions. Another strength of this

study is the prospective collection of data from real-world practice, from a very large number of consecutive patients with objectively confirmed DVT, in whom a diagnosis of recurrent VTE had been obtained by strictly applying objective criteria.

CONCLUSIONS

In summary, the rate of symptomatic PE or major bleeding during the first week of anticoagulant therapy was low (<1%), but 1 in every 4 such patients died. Thus, its clinical relevance should not be underestimated. We consistently found that in-hospital treatment does not confer any survival advantage over treatment at home. These data may help safely treat more DVT patients at home.

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AUTHOR CONTRIBUTIONS

Conception and design: FL, JT, MB, MS, MM
Analysis and interpretation: FL, JT, MB, PG, DB, MS, CF, MM
Data collection: FL, JT, MB, PG, DB, MS, CF, MM
Writing the article: FL, MM
Critical revision of the article: MS
Final approval of the article: JT, MB, PG, DB, MS, CF
Statistical analysis: JT
Obtained funding: MM
Overall responsibility: MM

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APPENDIX (online only).

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